14. (Amended) The method according to claim 11, wherein the [cytokine] G-CSF is administered before [the blocking agents] administering the anti-VLA-4 antibody or anti-VCAM-1 antibody.

REMARKS

The claims have been amended to more particularly point out and distinctly claim the subject matter of the invention. No new matter has been added, as full support for these amendments exists in the application as filed.

The Examiner has indicated that the application fails to comply with the sequence listing requirements since applicants have failed to request in writing that the CRF in the parent case be used. Applicants hereby request that sequence listing in the parent case be used in the presently pending application. The requisite statement and request are being submitted herewith. Therefore, applicants believe that the application is now in full compliance with all requirements.

Applicants have amended the specification to include a reference to the earlier filed application, and are submitting herewith an abstract of the disclosure. Additionally, applicants have amended the application to correct the references to the figures as described in the Brief Description of the Drawings. It is believed that these amendments have addressed the Examiner's concerns in paragraphs 1-6 of the Office Action.

Claims 1-14 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Applicants have amended the claims to more particularly point out and distinctly claim the subject matter of the invention, as well as to bring the claims into conformance with claim language in copending related cases, USSN 08/463,128 and 08/463,298, which have been allowed. It is believed that the amendments to the claims render the Examiner's rejections under the second paragraph of 112 moot.

The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide an adequate written description and an enabling specification commensurate with

the scope of the claims. Applicants have amended the claims such that the blocking agent is an anti-VLA-4 antibody, and the stimulating agent is a cytokine. Applicants submit that they have provided full support for antibodies as blocking agents and have submitted experimental data supporting a specific murine monoclonal anti-VLA-4 antibody, HP 1/2. Applicants believe that the specification clearly provides sufficient guidance for the use of antibodies as blocking agents as now claimed.

Additionally, without acquiescing in the Examiner's rejections, applicants have amended the claims to recite a specific stimulating agent in order to further the prosecution of this case. It is believed that the amendments to the claims obviate the Examiner's objections and rejections, and it is respectfully requested that they be withdrawn.

Additionally, claims 1-14 have been rejected under 112, first paragraph for the reasons set forth in the objection to the specification. As discussed above, it is believed that the amendments to the claims render the rejection of the claims and the objection to the specification moot.

Claims 1-3 are rejected under 35 U.S.C. 102 (a) as being anticipated by Simmons or Teixido. The Examiner states that both Simmons and Teixido disclose a method of using anti-VLA-4 antibodies to block the adhesion of CD34 cells to bone marrow stromal cells in vitro, which the Examiner has broadly interpreted to be a form of peripheralization. This rejection is respectfully traversed for the following reasons.

Teixido, as discussed in the specification, teaches various integrin interactions which are important for adhesion between bone marrow stromal cells and cells expressing high levels of CD34. The studies described in Teixido utilized antibodies to prevent the in vitro binding of stem cells to stromal cell monolayers. These studies did not examine the in vivo interactions within the bone marrow microenvironment that are involved in keeping the stem cells within that environment, or, whether such interactions can be reversed or perturbed to effect peripheralization of stem cells. Therefore, Teixido does

not teach or suggest this claimed invention related to the in vivo release of CD34 cells from the bone marrow into the peripheral blood.

Applicant's position that the in vitro data of Teixido does not teach that the same pathways are involved in the in vivo release of CD34+ cells from the bone marrow, is further supported by experimental data presented in the application. For example, applicants' data clearly demonstrates that the administration of antibodies to β2 integrin (which antibodies, according to Teixido, block the in vitro adhesion of CD34+ cells to stromal cells) does not cause peripheralization of CD34+ cells. See spec. p. 27, lines 1-23. Therefore, Teixido does not teach the presently claimed invention.

Simmons similarly does not teach the presently claimed invention. Simmons, as discussed in the specification, teaches only that, in an in vitro model, adhesion between stomal cells and CD34+ cells was predominantly dependent on the VLA-4/VCAM-1 interaction, and was largely inhibited by monoclonal antibodies to either VLA-4 or VCAM-1, with fibronectin playing a minor role in binding. Simmons does not, however, teach or suggest methods for the release of hematopoietic progenitor cells (i.e. CD34+ cells) from the bone marrow. Thus, Simmons does not teach the claimed invention directed to methods of peripheralization of CD34+ cells using antibodies as blocking agents of VLA-4.

Given the lack of teaching or suggestion in this reference about the mechanisms involved in the release of CD34+ cells from their in vivo microenvironment, on e of skill in the art could not have reasonably expected that the systemic administration of a blocking agent of VLA-4 would mobilize CD34+ cells from the bone marrow into the peripheral blood. Thus, it is respectfully submitted that this rejection is in error and should be withdrawn.

Claims 4-14 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Simmons or Teixido in view of Haas. The Examiner has stated that, although neither Simmons or Teixido teach the use of a stimulating agent in vivo, Haas teaches the in vivo use of GM-CSF in the preparation of hematopoietic stem cells. Therefore, the Examiner concludes that it would have been prima facie obvious to one of ordinary skill

in the art at the time the claimed invention was made to use in vivo administration of GM-CS, as taught in Haas, in the peripheralization method of either Simmons or Teixido. Additionally, the Examiner reasons that one skilled in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Haas, on the increased number of circulating stem cells that result from GM-CSF administration. This rejection is respectfully traversed for the following reasons.

The Examiner has not established a prima facie case of obviousness. The Examiner cannot base an obviousness rejection upon what a person skilled in the art might try, or might find obvious to try, but rather, must consider what the prior art would have led a person skilled in the art to do. The Examiner has attempted to establish both motivation to combine the references and an expectation of success for making the suggested combination of references. However, as discussed in more detail below, the Examiner has not provided sufficient expectation of success, nor has she established that the references, if combined would result in the claimed invention as a whole. At most, the Examiner has established motivation to try to combine the teachings of the various references, and obvious to try is not the standard.

As discussed above, Teixido does not teach or suggest methods for the in vivo release of CD34+ cells from the bone marrow into the peripheral blood. Simmons, teaches only that in an in vitro model, adhesion between stromal cells and CD34+ cells was predominantly dependent on the VLA-4/VCAM interaction. Simmons does not teach or suggest methods for the release of hematopoietic progenitor cells , i.e. CD34+ cells, from the bone marrow.

Haas, the secondary reference cited by the Examiner, relates only to the increase in the number of circulating progenitor cells in cancer patients who were administered recombinant human GM-CSF. Haas does not teach or suggest that blocking VLA-4 could cause the peripheralization of CD34+ cells. Thus, the secondary reference cited by the Examiner does not rectify the deficiencies of the primary references. Specifically, the references either alone, or in combination, do not teach or suggest the claimed invention as a whole, i.e. the in vivo peripheralization of CD34+ cells with anti-VLA-4 antibodies.

Given the lack of teaching or suggestion in this reference about the mechanisms involved in the release of CD34+ cells from their in vivo microenvironment, one skilled in the art could not have reasonably expected that the systemic administration of a blocking agent of VLA-4 would mobilize CD34+ cells from the bone marrow into the peripheral blood. Thus, none of the secondary references, even when combined with the primary references as suggested by the Examiner, teach or suggest the claimed invention as a whole. Therefore, applicants respectfully submit that this rejection is in error and should be withdrawn.

In light of the amendments and remarks above, it is respectfully submitted that this application is now in condition for allowance. Prompt and favorable notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned if it would be helpful in furthering the prosecution of this application.

Respectfully submitted,

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